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EDITORIAL COMMENT

Retrograde Coronary Perfusion: A Superior Route to Deliver Therapeutics to the Heart?*

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As the genomics and proteomics revolutions progress and the molecular biology of various cardiovascular pathologies is better understood, an increasing number of potential molecular therapies are being proposed. The ultimate success of any of these therapies depends upon many factors, including the biological activity of the therapeutic agents and the ability to deliver them to the proper cellular targets. Some of these agents may be effective when delivered systemically, whereas others may be safer and/or more effective when delivered locally. The use of drug-eluting stents to deliver anti-restenosis agents directly to targeted coronary segments is an excellent example of an effective "marriage" of a bioactive agent and an optimized local delivery strategy (1). In this issue of the *Journal*, von Degenfeld et al. (2) describe the use of an alternative delivery technique, retrograde coronary venous perfusion (RCVP), to deliver the angiogenic protein fibroblast growth factor-2 (FGF-2) to ischemic porcine hearts.

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Several strategies have been used to deliver angiogenic factors to the heart (3–10). The broadest division of these strategies is between the delivery of angiogenic genes or of intact angiogenic proteins (11,12). The intuitive argument for angiogenic gene therapy is based partially on the fact that most angiogenic proteins have a very short in vivo half-life. The gene therapy argument states that the only way to ensure exposure of the heart to sufficient angiogenic protein for a sufficient duration to produce therapeutic angiogenesis is by local production of the protein after gene delivery. The failure of two placebo-controlled angiogenic protein delivery clinical trials to meet pre-determined efficacy end points has supported this position (13,14). As controlled clinical data accumulates from angiogenic gene therapy trials, however, it appears that even sustained exposure to a single angiogenic gene product may not be enough to replicate the remarkable therapeutic benefits documented in preclinical animal studies, despite some evidence of effect (15,16). The biology of angiogenesis is quite complex, and optimal therapeutic stimulation of angiogenesis may require multiple factors or splice variants (17). Thus, both the questions of optimal delivery strategy and optimal therapeutic agent(s) remain open.

Anterograde intracoronary (IC) delivery of FGF-2 has been previously shown to yield relatively poor myocardial delivery and may explain in part why an IC FGF-2 clinical trial was disappointing (13,18). Anterograde IC delivery of the FGF-5–encoding adenovirus was, however, shown to effectively induce therapeutic angiogenesis in a porcine ameroid ischemia model, and this approach is now in phase III clinical testing (4,15). Despite the preclinical success of this IC adenovirus delivery approach, the degree of gene delivery to the myocardium achieved in this manner is quite variable and most often quite low. The endothelium of the coronary microvasculature is continuous and presents a formidable barrier to the passage of macromolecules, such as viral vectors, to the myocardium. This barrier function can be partially overcome with mechanical maneuvers that increase anterograde perfusion pressure and by pharmacologic methods that increase vascular permeability (19,20). To date, none of these methods has been readily adaptable to percutaneous delivery of therapeutic agents in the cardiac catheterization lab. The retrograde perfusion technique used by von Degenfeld et al. (2) may be a cath lab-friendly technique that overcomes some of the limitations of intracoronary delivery.

In their study, von Degenfeld et al. (2) used covered stents in a novel percutaneous approach to induce ischemia in the left anterior descending artery territory of pigs. They then tested the ability of RCVP of FGF-2 protein to induce angiogenesis and ameliorate myocardial ischemia in these pigs. Although complete resolution of perfusion and function defects was not achieved, retrograde infusion of FGF-2 did improve both flow and function in these animals, induced increased capillary density, and was more effective than anterograde infusion of FGF-2. Using radiolabeled FGF-2 protein, the authors demonstrated an over twofold increase in the amount of FGF-2 delivered to the heart with retrograde infusion versus anterograde. This may explain in part why this delivery route achieved more effective restoration of flow and function. Another possible explanation put forth by the investigators is that retrograde infusion results in a different distribution of FGF-2 delivery that is more biologically effective. In either case, the results are thought provoking and support further studies of retrograde infusion.

Retrograde coronary venous perfusion via coronary sinus cannulation has been an established method for the infusion of cardioplegic solution in cardiac surgery for many years. The use of this route for the delivery of therapeutic agents has also been previously reported, including retrograde

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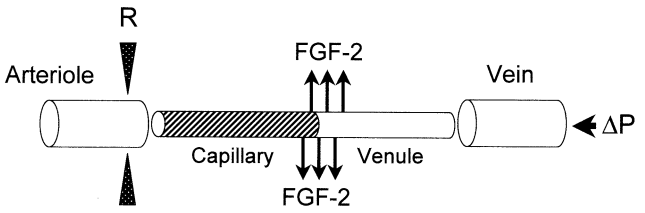

Figure 1. Retrograde coronary venous perfusion at increased pressure augments egress of macromolecules from coronary venules and capillaries. To accomplish retrograde coronary venous perfusion, the coronary sinus or a large cardiac vein is cannulated, balloon occluded, and perfused retrograde at a pressure slightly higher than systolic venous occlusion pressure (ΔP). Because the only resistance to this increased pressure is on the arterial side of the capillary-venule segments (R), the pressure within the capillaries and venules increases. This increased pressure facilitates translocation of macromolecules (e.g., fibroblast growth factor [FGF]-2) across the endothelium and into the myocardium.

infusion of nonrecombinant tissue-type plasminogen activator for coronary thrombolysis and delivery of L-arginine to reduce infarct size (21,22). Recently, RCVP was shown to be effective in the delivery of plasmid deoxyribonucleic acid (DNA) to the heart (23). The reason RCVP appears to yield more efficient myocardial delivery of proteins and plasmid DNA than anterograde infusion is theorized to be due to the lack of a so-called "resistance" vessel segment between the infusion catheter and the capillary–venule segment through which egress of the therapeutic agent is thought to take place. Thus, RCVP at mildly elevated perfusion pressures results in increased transvascular pressure in the capillary-venule segments and promotes passage of molecules across or through the endothelium. This is shown diagrammatically in Figure 1.

Whether or not RCVP will be applicable to clinical angiogenic therapy is presently unclear. Protein technology is evolving and it is possible that the combination of sustained-release protein preparations and RCVP will increase the therapeutic efficacy of angiogenic protein delivery, especially with newer protein agents, such as PR39, that appear to have greater angiogenic potential (24). The potential to use RCVP for gene delivery is also intriguing. Currently, direct intramyocardial injection of plasmid DNA or viral vectors encoding angiogenic factors is the most widely used method to deliver angiogenic genes (7,8). To establish RCVP as the preferred route for angiogenic gene delivery, superior ease of use or greater efficacy relative to either direct intramyocardial injection or anterograde IC infusion must first be demonstrated. Other considerations include the ability of RCVP to deliver agents to the right coronary territory, the variability of coronary venous drainage among patients, and the consistent safety of the procedure. Coronary sinus rupture is a known complication of coronary sinus retroperfusion (25). However, RCVP does appear to have the potential to be a clinically relevant route to deliver molecular therapeutics to the heart.

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